REMARKS

As a preliminary matter, Applicants' representative and Assignee's representative thank the Examiner for courtesies extended during the telephonic interview of August 21, 2007. During the interview, the rejections of record were discussed and possible means for overcoming the rejections. Applicants agreed to submit the present amendment and remarks.

By the present communication, claims 42, 43, 52, and 69-92 are canceled without prejudice and claims 93-109 are added. No new matter is added by the amendment. Support for the new claims may be found throughout the application as filed, including but not limited to the following:

Claim	Support
93	Original claim 42; paragraphs 283, 288, 289, 296, 298, 302, 307, and 308
94	Paragraph 295.
95, 96	Paragraph 297
97	Paragraph 301
98	Paragraph 305
99	Paragraph 306
100, 101	Paragraph 307
102	Paragraph 309
103. 107-09	Original claim 43, Example 166
104-106	Paragraphs 11-13, and 753; Table 6

In view of the foregoing amendments and the following remarks, reconsideration of the application is respectfully requested.

I. Rejection Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 42-43, 52 and 69-92 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is summarized as: "The instant specification does not adequately describe the nexus between the modulation of the specific tyrosine kinases (i.e. c-Kit among others[)] and a useful treatment of a disease/condition." As the pending claims have been canceled, the rejection is moot with respect to these claims. With regard to new claims 93-109, Applicants respectfully submit that the claims comply with the written description requirement for the reasons provided below.

First, Applicants note that the pending claims do not recite inhibiting a tyrosine kinase, rendering moot the Office's reasoning with respect to the alleged lack of nexus between the modulation of the specific tyrosine kinases (i.e. c-Kit among others[)] and a useful treatment of a disease/condition.

Second, Applicants respectfully submit that there is no basis in law for requiring a showing of nexus to demonstrate written description of claimed subject matter. To satisfy the written description requirement a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F. 3d 1306, 1319, (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d 1555, 1563 (Fed. Cir. 1991). An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F. 3d 1565, 1572 (Fed. Cir. 1997). An analysis of compliance with the written description requirement is conducted from the standpoint of one of skill in the art at the time the application was filed. See, e.g., *Wang Labs. V. Toshiba Corp.*, 993 F.2d 858, 865 (Fed. Cir. 1993). The present claims meet these standards.

New claims 93-109 are directed to the treatment of specific cancers, such as acute myelogenous leukemia, using a highly related group of compounds of Structure I. The application expressly recites each of the claimed cancers (e.g., at paragraphs 11-13 and 753) and provides *in vitro* and *in vivo* data supporting efficacy of treating the recited cancers with the claimed compounds (e.g., paragraphs 723-769) for many of the cancers. The Application also expressly supports the claimed genuses of compounds (see list on page 10 of this response) and the individual compound (4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, Example 166) which is the subject of claims 103 and 107-109. Thus, the application provides extensive description supporting the claimed invention and hundreds of working examples in the form of compounds synthesized and assayed, both in vitro and in vivo and has provided especially complete description with regard to the compound of Example 166. Accordingly, Applicants submit that one of ordinary skill in the art would recognize that the inventors had possession of the claimed invention at the time of filing.

B. Enablement

Claims 42-43, 52 and 69-92 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In support of the rejection, a Wands analysis is set forth in the Office Action on pages 4-8 and additional reasons are provided on pages 8-11. As the pending claims have been canceled, the rejection is moot with respect to these claims. With regard to new claims 93-109, Applicants respectfully submit that the claims comply with the enablement requirement for the reasons provided below.

First, the breadth of the present claims and the nature of the invention supports enablement of the claims. Claims 93-109 are directed to the treatment of specific cancers, such as acute myelogenous leukemia, using a highly related group of compounds of Structure I. The assertions made by the Office in the pending Action are simply inaccurate with respect to the scope of the present claims. For example, at page 8, line 11-12 it is stated that "the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease." The Office further states on page 9, lines 11-12 that "the new claims are drawn

to a method of treating all cancers." In fact, claims 93-109 are not directed to the treatment of any disease or all cancers, but recites a select group of specific cancers. Furthermore, claims 104, 105 and 106 recite subsets of these cancers which are the subject of the working examples at, e.g., paragraphs 753-768. Applicants also note that the specification discloses not only how to make the compounds (paragraphs 463-502) recited in the claimed methods, but discloses over 1000 compounds that were actually made (paragraphs 503-720 and Table 1). Hundreds of these compounds (paragraph 769, pp. 440-451) were tested using the assays described in the specification. Hence, the breadth and nature of the claimed invention is commensurate with the disclosure of the specification.

Second, the level of predictability in and the state of the art support enablement of Applicant's claims. As set forth in the response filed 3/16/2007, on pages 28-32, Applicants presented 10 peer-reviewed scientific articles showing the state of the art with respect to the correlation between the inhibition of various receptor tyrosine kinases, inhibition of angiogenesis and the treatment of cancer. Of particular interest with respect to the present claims, these articles show that inhibition of receptor tyrosine kinases lead to inhibition of tumor growth in acute myelogenous leukemia (AML) (Levis et al.); mast cell leukemia, germ cell tumors, small-cell lung carcinoma, gastrointestinal stromal tumors (GIST), acute myelogenous leukemia, neuroblastoma, ovarian carcinoma and breast carcinoma (Heinrich et al.); AML and chronic myelogenous leukemia (CML) (Smolich et al.); neuroblastoma (Berwanger et al.); T-cell leukemias (Majolini, et al.); CML and GIST (Pietras et al.); and breast cancer (Valtola et al.). This evidence of the state of the art and level of unpredictability remains unrefuted by the cell culture articles cited by the Office. Even if it were true that "cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the inv vivo environment involved in host-tumor and cell-cell interaction," this does not negate the known correlation between in vitro inhibition of receptor tyrosine kinases and inhibition of cancer growth, and by itself cannot compel a conclusion that undue experimentation is needed to practice the claimed methods.

Furthermore, Applicants have provided ample guidance for practicing the claimed methods without undue experimentation. As set forth on pages 32-36 of Applicants response, dated 3/16/2007, the application provides extensive biological data supporting the claimed methods. However, the Office asserts that "in vitro testing for cancer treatment in multiple cancer cell lines is not accepted as predictive of in vivo activity." This is simply not correct.

First, this statement implies that Applicants have no *in vivo* data. This is not the case as Applicants discussed at pages 34-36 of the 3/16/2007 response. The *in vivo* data is set forth again below for the convenience of the Office. Second the cell culture data in conjunction with the *in vivo* data in the application are exactly the types of data that the Food and Drug Administration (FDA) accepted as predictive of anti-cancer activity in humans when it approved human clinical trials of the compound of Example 166 for acute myelogenous leukemia. The latter cancer is one of the cancers recited in the claimed methods. Applicants respectfully submit that the data provided by Applicants are therefore sufficiently predictive for the skilled artisan to practice the claimed methods without undue experimentation, and that the claimed methods comply with the enablement requirement.

The in vivo data set forth in the application was discussed as follows in the response, dated 3/16/2007.

Specifically, *in vivo* daily oral dosing with the compound 166 resulted in significant anti-tumor activity in a broad range of human and mouse models as explained in the following passage taken from paragraph 760 of the application,

> [0760] *In vivo* daily oral dosing of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one resulted in significant anti-tumor activity in a broad range of human and murine tumor models. Established tumor xenografts of prostate, colon, ovarian and hematologically-derived cancer cells have all demonstrated responsiveness to treatment in a dose-dependent manner, with ED_{50s} ranging from 4-65 mg/kg/d. The *in vivo* activity ranges from growth inhibition to stable disease and tumor regressions. For example, the compound induces regression and growth inhibition in subcutaneous KM12L4a human colon tumor xenografts in *nu/nu* mice. FIG. 1 shows tumor volume over time at various doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Dosing started when tumor xenografts

reached 125 mm^3. The results show significant tumor growth inhibition after 4 doses of greater than or equal to 30 mg/kg, and tumor regressions at 60 and 100 mg/kg. Similar results were observed in 90-100% of animals with larger KM12L4a colon tumor xenografts. Treatment started when tumor size reached 500 and 1000 mm^3. Tissue concentration studies showed that 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was retained in the tumor with levels up to 65-300 fold higher than plasma at 24 hours after dosing. In addition, target modulation studies showed inhibition was maintained for more than 24 hours.

Further evidence of the *in vivo* anti-cancer therapeutic properties of the compounds of the invention as illustrated by compound 166 of the present application is described in paragraph 761 and shown in Figure 12. MV4-11 tumor cells were implanted in the flank of irradiated SCID-NOD mice. Tumors were then allowed to grow to 300, 500, or 1000 mm^3 before treatment was initiated with daily oral dosing at 30 mg/kg/day. The compound corresponding to Example 109 of the present application displayed an ED_{50} of 4 mg/kg/day in this tumor model in SCID-NOD mice, and a dose of 30 mg/kg/day inhibited the growth of larger MV4-11 tumors by 86% for tumors of 500 mm^3 volume at start of treatment and by 80% for tumors of 1000 mm^3 volume at start of treatment. Several complete regressions were also observed. Regressions were found to be stable after cessation of dosing. In those tumors that recurred, a second cycle of 30 mg/kg/day dosing of the compound again caused partial regression, indicating a lack of acquired resistance to the compound.

In a tumor metastasis study in which 4T1 murine breast tumor cells were implanted subcutaneously in BALB/c mice, compound 166 of the present application inhibited the primary tumor up to 82% and inhibited liver metastasis by more than 75% at all doses above 10 mg/kg/day as described in paragraph 762.

The present application also discloses evidence of the anti-angiogenic effects of inventive compounds. Figure 2 shows the results of an *in vivo* bFGF driven murine matrigel model of neovascularization. The bFGF supplement induces blood vessel formation (neovascularization or angiogenesis) that can be quantified by measuring the hemoglobin levels in the matrigel plugs following their removal from the animals. In these studies, mice were first implanted with the

matrigel plug containing the bFGF and then orally dosed for 8 days with varying amounts of 4-amino-5-fluoro-3-[5-(4-methylpiperazinyl-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, a compound representative of those disclosed in the present application (Example 109 of the present application). The plugs were then removed, and the hemoglobin concentrations were measured. As shown in Figure 2, significant inhibition of angiogenesis was observed, with an ED_{50} of 3 mg/kg/day (ED_{50} is defined as the dose that effectively inhibits angiogenesis by approximately 50%). Furthermore, all doses were well tolerated by the animals in the 8-day studies. Additional evidence of an anti-angiogenic effect is presented in Figure 10, which shows inhibition by 4-amino-5-fluoro-3-[5-(4-methylpiperazinyl-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in an *ex vivo* rat aortic ring assay.

As still further evidence of the guidance provided in the present application, Applicants direct the Examiner's attention to paragraph 441 of the application where it is noted that compounds of the invention can also be administered in conjunction with other anti-cancer drugs. Confirmatory evidence of the synergistic effect of compounds of the invention with other anti-cancer drugs is presented at paragraph 766 which describes studies using cytotoxic agents such as CPT-11 (Irinotecan) and 5-FU in combination with compound 166 in the KM12L4a colon and other tumor models. As described in paragraph 766, and shown in Figures 5-8,

> Combination therapy studies were done using the standard cytotoxics, irinotecan and 5-FU, in the KM12L4a colon tumor model. Significant potentiation of activity was seen, with the most dramatic effects at low, inactive doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one as shown in FIG. 5. A cyclic dosing regimen of the compound at 50 mg/kg in combination with irinotecan gave excellent results, with 3 complete regressions and 7 partial regressions, as shown in FIG. 6. Synergistic and greater than additive effects were also seen with trastuzumab combined with 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the erbB2-overexpressing ovarian tumor model, SKOV3ip1 (see FIG. 7). Additionally, tumor responses and regressions were significantly improved over each single agent treatment in the A431 epidermoid tumor model when 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was combined with ZD1839 (Iressa) (see FIG. 8). These data suggest that 4-

amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has the potential to be a broadly applicable and effective therapy for solid and hematological cancers.

Further, Applicant draws the Examiner's attention to three references submitted herewith describing *in vivo* studies on compound 166. This compound, which is the subject of claims 43, 83, and 89 [now claims 103, 107, 108 and 109], is currently undergoing Phase II clinical trials after undergoing separate Phase I clinical trials for multiple myeloma (MM) and acute myelogenous leukemia (AML), as well as one for mixed solid tumors. The three references show tumor regression and in-vivo target modulation of receptor tyrosine kinases in colon cancer, MM, and AML cells. Particularly, in MV4;11 tumors, target modulation of pFLT3, pSTAT5 and pERK was achieved with compound 166, and tumor regressions and eradication of AML cells from bone marrow were shown in s.c. and bone marrow engraftment leukemic xenograft models. Clin Cancer Res 2005;11 (14) p.5281-91. In a separate colon cancer study, immunohistochemical analysis showed reduction of phosphorylated PDGFB and pERK in tumor cells after oral dosing of the compound 166, accompanied by a decreased tumor cell proliferation rate and reduced intratumoral microvessel density. Clin. Cancer Research 2005;11 (10) p.3633-41. Finally, in primary myeloma cells from t(4;14) patients, compound 166 inhibited downstream extracellular signal-regulated kinase phosphorylation and further displayed therapeutic efficacy in a xenograft mouse model of FGFR3 MM. Blood. 2005:105 p.2941-48.

II. Rejections Under 35 U.S.C. § 102

Claims 42-43, 52 and 69-92 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Nos. 6,605,617 and 6,800,760, and under 35 U.S.C. § 102(a) as allegedly being anticipated by U.S. Patent No. 6,605,617, WO 2002/0107392 and WO 200222895. As the pending claims have been canceled, the rejection is moot with respect to these claims. With regard to new claims 93-109, Applicants respectfully submit that the new claims are not anticipated by the cited references for the reasons provided below.

The cited references fail to teach all of the elements of the claimed methods. First, none of the references expressly discloses any of the recited cancers. Second, the references do not inherently disclose the claimed methods because said methods do not necessarily flow from the disclosed administration of VEGF inhibitors to a subject. A method is not a composition with inherent properties. The burden in demonstrating inherency is a high one, and a method of treating acute myelogenous leukemia, for example, does not necessarily flow from the general teachings of the cited references. Accordingly, Applicants respectfully submit that the claimed methods are novel over the cited references.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be addressed in view of the present amendment and reply, the Examiner is requested to call the undersigned at the telephone number provided herein so that a prompt disposition of the application can be achieved.

Respectfully submitted,

Date October 11, 2007

By _____

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